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Association of Ectopically Produced Hyperparathyroidism With Hepatoma

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THERE HAVE BEEN MANY REPORTS of hypercalcemia associated with malignant disease in patients in whom there was no apparent dysfunction of the parathyroid glands at surgical exploration or autopsy, and no bony metastasis. This association has been noted with a wide variety of malignant tumors.[1] Albright and Reifenstein[2,3] first suggested the possibility of non-glandular tumor producing a parathyroid-like hormone in a patient with renal cell carcinoma and bony metastasis in whom hypophosphatemia could not be explained. Connor et al[4] and Plimpton and Gellhorn[5] reported hypercalcemia in patients with malignant disease in whom serum calcium levels fell to normal with removal of the primary tumor. In 1962 Fry[6] first proposed the term *pseudohyperparathyroidism* to describe the syndrome of hypercalcemia and hypophosphatemia without skeletal metastasis in patients with non-parathyroid malignant tumors. Tashjian et al[7-9] reported successful extraction of immunochemically active substance from malignant tumors by use of complement fixation inhibition techniques. Utilizing radioimmunoassay, Sherwood et al[10] later provided quantitative and physical-chemical characterization of the tumor substance. With more recent refinements of assay, Roof et al[11] demonstrated immunological differences between the parathyroid hormone in the serum of patients with primary hyperparathyroidism and that in the serum of some patients with ectopic hyperparathyroidism.

Thus, fall of serum calcium levels with irradiation or removal of malignant tumors, recurrence of the hypercalcemia with recurrence of the tumor, elevated parathyroid-like hormone activity in the serum of these patients, and assay of extracts of such tumors for hormone activity all give evidence that these tumors are capable of synthesizing metabolically active hormones.

Lafferty[1] in his extensive review of "pseudohyperparathyroidism" of malignant disease suggested that one of the following criteria be met for confirmation of this syndrome: (1) absence of radiographic and postmortem evidence of bone metastasis and absence of parathyroid adenoma at surgical exploration or postmortem examination, (2) significant reduction of calcium following resection of tumor, or (3) positive parahormone immunoassay of a neoplasm extract.

We reviewed the data on all previously reported cases of this syndrome associated with primary liver tumors which met one of the foregoing criteria. In addition we present two new cases of this syndrome; in one the tumor was a hepatocellular carcinoma and in the other an adenocarcinoma of the intrahepatic biliary tract.†

Reports of Cases

Case 1. The patient was a 58-year-old Negro man who was referred with history of progressive weakness, lethargy, and a 20-pound loss in weight. He had previously been treated for alcoholic liver disease with ascites and jaundice. He had a long history of alcoholism and of heavy cigarette-smoking. There was no pertinent family history. The patient denied fever, chills, night sweats, cough, chest pain, dyspnea, change in bowel habits or abdominal complaints. On physical examination he appeared older than his stated age. Blood pressure was 110/90 mm of mercury, pulse 82, temperature 37°C (98.6°F) and respirations 18 per minute. There was conjunctival icterus. On examination of the chest the diaphragm was found to be elevated on the right side. The heart was not enlarged, and no murmurs, rubs or gallops were heard. The edge of the liver was three fingerbreadths below the right costal margin in

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Case 2 was provided by David Potyk, M.D., Assistant Clinical Professor of Medicine, USC School of Medicine, Los Angeles, California.

the mid-clavicular line, and the vertical liver span along the anterior axillary line was 17 cm. Contiguous with the hard, firm edge of the liver was a firm, smooth, non-tender 15 x 15 cm epigastric mass. On rectal examination the prostate gland felt normal. The extremities were wasted.

Laboratory values included the following: hematocrit 38 percent; platelets normal range; leukocytes 8,900 per cu mm with a normal differential. The urine showed urate crystals and was positive for bilirubin. Serum sodium was 130 mEq, potassium 4.2 mEq, bicarbonate 35 mEq, chloride 90 mEq, glucose 74 mg per 100 ml and blood urea nitrogen was 31 mg per 100 ml. Prothrombin time was 90 percent. The albumin was 2.9 grams, globulin 7.1 grams, total bilirubin 3.0 mg, and indirect bilirubin 1.3 mg per 100 ml. Calcium levels were serially greater than 12.0 mg per 100 ml (normal range 9 to 11 mg). Inorganic phosphate was consistently below 2.5 mg per 100 ml (normal range 2.6 to 4.5 mg). Alkaline phosphatase was 5.5 BL units on admission and 2.7 BL units on discharge. The uric acid was 11.3 mg and creatinine 1.3 mg per 100 ml; SGOT 140, SGPT 20, CPK 1.9 and LDH 400 units; serum iron was 69 and TIBC 297 mcg per 100 ml, and iron saturation was 23 percent. Triiodothyronine by uptake was 10.3 percent, and tetraiodothyronine by CPB was 4.6 mcg per 100 ml. Serum protein electrophoresis was normal, and the urine showed no Bence-Jones protein. Hepato-fetoglobulin was positive. An x-ray film of the chest showed a high right hemidiaphragm and no evidence of active or metastatic disease. An x-ray film of the abdomen showed hepatomegaly. An upper gastrointestinal series with small bowel follow-through, a barium enema series and proctoscopic examinations showed no abnormalities. Liver scan demonstrated a filling defect corresponding to the left lobe. Liver biopsy was read as hepatocellular carcinoma. A long bone series, metastatic series, a bone scan and an intravenous pyelogram showed no lesions. The patient was discharged to the oncology service and was readmitted two weeks later with an upper gastrointestinal hemorrhage. He eventually died of pneumonia. Postmortem findings confirmed the presence of hepatocellular carcinoma. No evidence of metastasis was found. The patient was also found to have tuberculous pneumonia. All four parathyroid glands were isolated and found to be histologically normal.

Case 2. The patient, a 36-year-old white man, was admitted initially with complaints of weight loss of 100 pounds, abdominal pain and weakness for five or six months. The pain was mainly in the right upper abdominal quadrant, and it was aggravated by motion or by food. Past medical history was not remarkable except for the drinking of two quarts of beer and a pint of whiskey a day. Family history and review of systems were not significant. On physical examination the patient was normotensive, afebrile, obese and lethargic. There was no jaundice or conjunctival icterus. The liver edge was palpable 3 cm below the right costal margin in the mid-clavicular line, and the spleen was palpated 4 cm below the left costal margin in the left axillary line. Hemoglobin was 12 grams per 100 ml and the hematocrit was 37 percent. Leukocytes were normal in number and differential. Prothrombin time was 75 percent. Electrolytes and fasting blood sugar were normal. Bromsulphalein retention was 13.5 percent. Urinalysis showed pyuria and cast formation but no bacteria. Serial serum calcium determinations were 13.1, 13.5, 12.7, 14.9, and 13.8 mg per 100 ml (normal range 9-11 mg). Inorganic phosphate levels were 2.6 to 2.3 mg per 100 ml. Results of x-ray examination of the chest, barium enema, intravenous pyelogram and survey for metastasis to bone were normal. Repeated cholecystograms failed to demonstrate the gallbladder. Needle biopsy of the liver showed adenocarcinoma. The patient was discharged and treated as an outpatient with 5-fluorouracil and prednisone. Because of progressive weight loss, weakness, and edema, he was readmitted one month later. Physical examination at that time revealed additional massive ascites and three-plus pitting pretibial edema. The blood urea nitrogen was 31 mg, albumin 1.9 grams, globulin 4.5 grams and total bilirubin 4.7 mg per 100 ml. Alkaline phosphatase was 29.6 King-Armstrong units. Serial serum calcium determination was 12.7, 14.1, and 14.6 mg per 100 ml, and prosphate was 2.7 per 100 ml. The patient's condition deteriorated rapidly, and he died 11 days after admission. At postmortem primary adenocarcinoma of the liver was found. Review of the slides showed adenocarcinoma of the intrahepatic biliary tract. No metastatic lesions could be found. The four parathyroids and thyroid gland were found to be histoligically normal.

TABLE 1.—*Review of Case Reports of Ectopically Produced Hyperparathyroidism Associated with Hepatomas*

Reference	Age Sex	Serum Ca^{++}	Serum Phos.	Albumin	AP*	Bone Scan	Parathyroids No.**	Parathyroids Descrip.	Ca^{++} after tumor removal	Hormone assay tumor extract	Tissue Diagnosis
1953[14]	74m	11.5-15.6	2.6-5.0	4.1-5.4	14	NP	3	N	NP	NP	hepatic hemangiosarcoma
1963[15]	52m	10.6-13.2	2.2-3.6	2.7-3.9	22-36	NP	0	—	NP	NP	hepatic cholangiocarcinoma
1965[16]	23m	20.2	4.4	4.3	35	NP	4	N	NP	NP	hepatocellular carcinoma
1968[17]	57m	9.0-25.0	1.3-3.4	1.0-2.7	17-25	NP	2	N	NP	NP	hepatic cholangiosarcoma
1970[18]	56m	10.0-17.6	1.4-2.7	—	20-40	N	3	N	↓	+	intrahepatic biliary adenocarcinoma
1971[12,13]	—	—	—	—	—	—	—	—	—	—	hepatocellular (3), hepatoma (1)
Case 1	58m	10.5-12.4	2.2-2.6	2.7-2.9	9-19	N	4	N	NP	NP	hepatocellular carcinoma
Case 2	36m	12.7-14.9	2.3-2.6	1.9	29	NP	4	N	NP	NP	intrahepatic biliary adenocarcinoma

*converted to King-Armstrong units
**at surgical exploration or postmortem examination
NP—not performed
N—normal

Abbreviations

BL	**Bessey-Lowry units**
SGOT	**serum glutamic oxalic transaminase**
SGPT	**serum glutamic pyruvic transaminase**
LDH	**lactic dehydrogenase**
TIBC	**total iron-binding capacity**
CPK	**creatine phosphatase**
CPB	**competitive protein binding**
PTH	**parathyroid hormone**

Discussion

Search of the literature revealed five previously recorded case reports of hypercalcemia associated with malignant liver tumors which satisfied the criteria mentioned above. In addition, Riggs et al[12] included four cases of hepatoma in a recent report. Three of these were hepatocellular carcinoma, and the fourth was an undesignated hepatoma.[13] No additional data were given in the report concerning these patients.

Data from the previously reported cases and the present case reports are presented in Table 1. Of interest is the fact that all cases involved male patients.

In evaluating hypercalcemia, the following disease processes and diagnostic procedures should be considered: (1) milk alkali syndrome—history of alkali intake, (2) vitamin D intoxication—review medications, (3) immobilization—paralysis or external fixation by a cast, (4) hyperthyroidism, hypothyroidism—protein-bound iodine, radioactive iodine uptake, tetraiodothyronine by CPB, (5) bone disease—radiologic bone survey, bone scan, (6) sarcoidosis—lymphadenopathy, skin lesions, serum proteins, chest film, (7) adrenal insufficiency—17-OH steroids, (8) renal disease—creatinine clearance, intravenous pyelogram, (9) multiple myeloma, leukemia—serum protein electrophoresis, Bence-Jones protein, bone survey, bone marrow. Even with these diseases ruled out, the possibility of occult malignant disease with parathyroid-like activity should be thoroughly winnowed before consideration is given to exploration of the parathyroid glands.

Lafferty[1] pointed out the following items as weighing heavily toward the diagnosis of ectopic hyperparathyroidism: (1) presence of anemia, (2) elevated sedimentation rate, (3) weight loss, (4) recent onset, and (5) serum chloride less than 102 mEq per liter. The variety of tumors which produce PTH-like material occur in the fol-

lowing descending order of frequency: lung, kidney, colon, bladder, and ovary. The two cases herein reported point out the necessity of considering hepatic tumor among these.

Summary

Two cases of ectopically produced hyperparathyroidism associated with hepatoma are presented and previously reported cases of this syndrome are briefly reviewed.

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